

REMARKS

I. Status of the claims

Claims 1-30 are pending in this application. Claims 5, 16, and 27 have been withdrawn. No new matter has been added by this proposed amendment nor does this amendment raise new issues or necessitate the undertaking of any additional search of the art by the Examiner. All of the elements and their relationships now claimed were earlier claimed in the claims as examined and support for these amendments can be found on page 17, paragraph 2, of the specification. Moreover, Applicants' proposed amendments address the Examiner's concerns made in the Final Office Action mailed January 4, 2001. Therefore, this Amendment under 37 C.F.R. § 1.116 should allow for immediate action by the Office. The proposed amendments, moreover, place the claims in condition for allowance or, at least, in better form for appeal, if necessary.

Claims 1, 17, and 25, were amended in order to more clearly define the subject matter of the invention in response to the Examiner's indefinite rejection under 35 U.S.C. § 112, second paragraph. Furthermore, the scope of the claims were not intended to be narrowed by these amendments. The claims were simply amended to include the definition of "substantially homogenous" as defined in the specification.

II. Rejections under 35 U.S.C. § 112

In the Final Office Action dated January 4, 2001, (Office Action), the Examiner maintained the rejection of claims 1-16 and 25-30 under 35 U.S.C. § 112, second

paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to the Examiner, claims 1-16 and 25-30 are indefinite because it is unclear what is intended by the phrase "substantially homogenous size distribution". The Examiner indicates that in this context, the term "substantially" is a relative term which modifies the term "homogenous" and further states that the term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and the term does not specify an art-recognized quantity. In the Examiner's view, the term "substantially" renders indefinite the degree of homogeneity required by the claims.

Applicants respectfully traverse this rejection. Applicants maintain that the specification adequately defines the term "substantially homogeneous". However, with the sole purpose of expediting prosecution, Applicants have amended claims 1 and 25 to include the meaning of the phrase "substantially homogeneous" as defined in the specification. Support for these amendments can be found on the specification at page 17, ¶ 2. All remaining claims depend either directly or indirectly from claim 1 or claim 25. Therefore, Applicants respectfully request that these rejections be withdrawn.

The Examiner argues that claims 5 and 27 are incomplete because they require a size distribution of less than 20%, but fail to recite of what quantity or quality 20% is a fraction. Similarly, the Examiner states that claim 16 is indefinite because it requires a variation in size distribution of less than 20%, but fails to provide any standard from

which to calculate the 20% variation. Applicants have withdrawn claims 5, 16, and 27 from examination. Therefore, the Examiner's arguments are now moot.

The Examiner further argues that claims 25-30 recite the phrase "a substantially homogenous size distribution". In the Examiner's view, this phrase is indefinite because the specification does not provide a limiting definition.

Applicants respectfully disagree. However, as described above, Applicants have amended claim 25 further clarifying the meaning of the phrase "substantially homogeneous". Therefore, Applicants respectfully request that this rejection be withdrawn.

III. Rejections under 35 U.S.C. § 102

The Examiner maintained the rejection of claims 1-3, 5, 6, 9-11, 13, 14, 16-19, 21, 22, and 24-29 under 35 U.S.C. 102(b) as being anticipated by Harris et al. (U.S. Patent No. 5,719,131, issued February 17, 1998).

According to the Examiner, *Harris* teaches a method of making micellar complexes comprising a cationic lipid, a PEG derivatized colipid, and DNA. In response to Applicants' argument that *Harris* fails to teach micellar complexes of a substantially homogenous size distribution the Examiner states that because the specification fails to adequately define the phrase "substantially homogenous size distribution", and that a composition of micellar complexes made by the method of *Harris* is considered to have a substantially homogenous size distribution, absent evidence to the contrary.

Applicants respectfully traverse this rejection. Foremost, and as previously stated, Applicants maintain that the specification adequately defines the phrase substantially homogenous size distribution. However, in an effort to expedite prosecution, Applicants have amended the claims to recite this definition. Since *Harris* does not teach micellar complexes having a variation in size distribution of less than or equal to about 20% with respect to the mean size of the micellar complexes, Applicants submit that *Harris* does not teach all of the limitations of the instant claims and therefore does not anticipate them. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Claim 5 was included in the above rejection because, in the Examiner's view, the claim's limitation regarding size distribution is indefinite. Thus, according to the Examiner, absent evidence to the contrary, *Harris* also anticipates claim 5. Applicants have withdrawn claim 5 from examination. Accordingly, the Examiner's arguments are now moot.

The Examiner also included claims 6, 13, and 21 in the above rejection because in his opinion the methods and compositions covered by these claims do not appear to be distinguishable from the teachings of *Harris*. The Examiner states that the claims are drawn to micellar compositions coated with a hydrophobic species and that the specification teaches that these compositions are made by adding the hydrophobic species to the micellar compositions. According to the Examiner, this would seem to be inherent in the method of making the initial micellar compositions because the addition

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of lipid micelles to DNA would result in condensation of the DNA around cationic lipids, and any uncomplexed lipids would be available to coat the DNA.

Applicants respectfully disagree. However, as described above, the claims as amended are further distinguishable from the teachings of *Harris* because *Harris* does not disclose micellar complexes having a variation in size distribution of less than or equal to about 20% with respect to the mean size of the micellar complexes. Therefore, *Harris* does not teach all of the limitations of the instant claims and Applicants respectfully request that this rejection be withdrawn.

The Examiner also noted that Applicant's arguments filed on October 23, 2000, with respect to the meaning of the phrase "substantially homogenous size distribution" do not apply to claims 17-19, 21, 22, and 24, which do not recite that limitation.

Claim 17 has been amended to more clearly define the micellar complex to which it refers, incorporating the definition of micellar complexes of substantially homogenous size distribution. Since *Harris* does not disclose substantially homogenous micellar complexes, *Harris* does not teach all of the limitations of the instant claims as amended. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Examiner also maintained the rejection of claims 1-3, 6-14, 16-19, and 21-30 under 35 U.S.C. 102(e) as being anticipated by Unger (US Patent No. 6,028,066, filed May 2, 1997).

According to the Examiner, *Unger* teaches a method of making micellar complexes by combining micellar lipids with a bioactive agent, which may be DNA and wherein the micellar lipids may comprise PEG-modified lipids.

Applicants respectfully traverse this rejection. Similar to the teachings of Harris, Applicants submit that *Unger* does not teach all of the limitations of the instant claims and therefore does not anticipate them. *Unger* does not teach the preparation of micellar complexes having a variation in size distribution of less than or equal to about 20% with respect to the mean size of the micellar complexes. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Claim 5 was included in the above rejection because, in the Examiner's view, the claim's limitation regarding size distribution is indefinite. Thus, according to the Examiner, absent evidence to the contrary, *Unger* also anticipates claim 5. Applicants have withdrawn claim 5 from examination. Accordingly, the Examiner's arguments are now moot.

The Examiner also included claims 6, 13, and 21 in the above rejection because in his opinion the methods and compositions covered by these claims do not appear to be distinguishable from the teachings of *Unger*.

Applicants respectfully disagree. Applicants submit that claims 6, 13, and 21, are further distinguishable from the teachings of *Unger* because, as previously stated, *Unger* does not disclose micellar complexes having a variation in size distribution of less than or equal to about 20% with respect to the mean size of the micellar

complexes. Therefore, *Unger* does not teach all of the limitations of the instant claims and Applicants respectfully request that these rejections be withdrawn.

The Examiner also noted that Applicant's arguments filed on October 23, 2000, with respect to the meaning of the phrase "substantially homogenous size distribution" do not apply to claims 17-19, 21, 22, and 24, which do not recite that limitation.

Claim 17 has been amended to more clearly define the micellar complex to which it refers, incorporating the definition of substantially homogenous size distribution. Since *Unger* does not disclose substantially homogenous micellar complexes, *Unger* does not teach all of the limitations of the instant claims as amended. Accordingly, Applicants respectfully request that this rejection be withdrawn.

IV. Rejections under 35 U.S.C. § 103

The Examiner maintained the rejection of claims 1, 4, 15, and 20 under 35 U.S.C. 103(a) as being unpatentable over Harris et al (US Patent No. 5,719,131, issued February 17, 1998).

According to the Examiner, *Harris* teaches a method of making micellar complexes wherein 64 different cationic lipid suspensions were combined with equal volumes of 64 different DNA solutions. The Examiner states that among the mass ratios of lipid to DNA that were encompassed were 0.7:1, 1.4:1, 5.6:1, and 11.2:1, and that although *Harris* does not teach the combination of lipid and DNA in an 8:1 vol:vol ratio, this volume ratio would have been obvious in view of the fact that *Harris* could just as easily have used equimolar solutions of both lipids and DNA and added the

appropriate volumes of each to arrive at the range of mass concentrations taught by *Harris*. In the Examiner's view one would have been motivated in this instance to use a ratio of 8:1 vol:vol to achieve a lipid:DNA mass ratio of 8:1. The Examiner argues that one would have been motivated to achieve this ratio because the concentration of each of these components is a result-effective variable. That is, the results of a technique using the composition are affected by concentrations of each of these variables, and one of ordinary skill would be motivated to optimize the concentrations of each variable. The Examiner further states that in this case, the specification and claims disclose that ratios of 1:1 and 8:1 will yield the claimed compositions, and therefore, in the Examiner's opinion, the claimed ratio of 8:1 does not appear to be absolutely required for the function of the invention. Finally, the Examiner indicates that *Harris* teaches ratios covering the range of ratios disclosed as functional by Applicant and that discovering the optimum or workable ranges by routine experimentation would not be inventive.

Applicants respectfully traverse this rejection. As described above, the claims have been amended to recite the definition of a micellar complex that has a substantially homogenous size distribution.

Since the Examiner has failed to provide the motivation one skilled in the art would have to modify the teachings of *Harris* to arrive at the instant invention as claimed, *Harris* does not render the presently claimed invention obvious. Accordingly, the Patent and Trademark Office has not established a *prima facie* case of obviousness and therefore Applicants respectfully request that this rejection be withdrawn.

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V. Conclusions

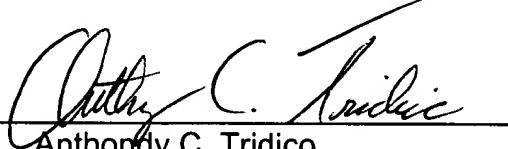
In view of the foregoing remarks, Applicants submit that this claimed invention, as amended, is neither anticipated nor rendered obvious in view of the prior art references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and reexamination of the application, and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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APPENDIX TO AMENDMENT OF APRIL 4, 2001

AMENDMENTS TO THE CLAIMS

1. A method of making micellar complexes comprising:
 - a) combining at least one cationic lipid with a sufficient amount of PEG derivative to produce micellar lipids;
 - b) combining said micellar lipids and at least one biologically active molecule to form said micellar complexes,wherein **[said micellar complexes have a substantially homogenous] the variation in size distribution of said micellar complexes is less than or equal to about 20% with respect to the mean size of said micellar complexes.**

17. A method of delivering a biologically active molecule to a cell of a mammal comprising contacting said cell with a composition comprising a micellar complex, wherein said micellar complex comprises:
 - at least one cationic lipid;
 - at least one biologically active molecule; and
 - a least one PEG derivative**and wherein said micellar complex is part of a group of micellar complexes having a variation in size distribution of less than or equal to about 20% with respect to the mean size of said group of micellar complexes.**

25. A micellar complex comprising:
- at least one cationic lipid;
 - at least one PEG derivative; and
 - at least one biologically active molecule;
- wherein a group of said micellar complexes have a **[substantially homogeneous]** size distribution of less than or equal to about 20% with respect to the mean size of said micellar complexes.

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